Cerebellar Ataxia With Anti–Glutamic Acid Decarboxylase Antibodies

Study of 14 Patients

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Background: Antibodies to glutamic acid decarboxylase (GAD-Ab) are described in patients with insulin-dependent (type 1) diabetes mellitus (IDDM), in stiff-man syndrome, and, recently, in a few patients with cerebellar ataxia.

Objectives: To show a link between GAD-Ab and some patients with cerebellar ataxia and to clarify their clinical and immunologic profiles.

Methods: Serum samples were selected from 9000 samples of 4 laboratories. The selection criterion was an immunohistochemical pattern compatible with GAD-Ab that was confirmed by radioimmunoassay. We identified 22 patients with stiff-man syndrome and 14 with cerebellar ataxia and GAD-Ab.

Results: Thirteen of the 14 patients with cerebellar ataxia and GAD-Ab were women, and 11 had late-onset IDDM. Patients did not have clinical or radiologic evidence of brainstem involvement. Ten patients had oligoclonal IgG bands in the cerebrospinal fluid, and intrathecal GAD-Ab synthesis was observed in 5 of the 6 patients studied. The level of GAD-Ab of these patients was similar to those with stiff-man syndrome and significantly higher than those with IDDM or with polyendocrine autoimmunity (P<.001). However, the GAD-Ab levels of 6 of the 9 patients with polyendocrine autoimmunity overlapped with those of patients with cerebellar ataxia.

Conclusions: These results suggest a link between high level of GAD-Ab and some cases of cerebellar ataxia, particularly women with IDDM. If high serum levels of GAD-Ab are detected, the cerebrospinal fluid should be evaluated for the presence of oligoclonal IgG bands and intrathecal synthesis of GAD-Ab to further prove an autoimmune origin of the syndrome.

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LUTAMIC acid decarboxylase (GAD) is a major enzyme of the nervous system that catalyzes the conversion of glutamate to γ-aminobutyric acid (GABA). This enzyme, also expressed by pancreatic beta cells, has been identified as a dominant and essential autoantigen in the development of insulin-dependent (type 1) diabetes mellitus (IDDM).\(^1\) Anti-GAD autoantibodies (GAD-Ab) are present in up to 80% of patients with newly diagnosed IDDM and can be detected many years before the clinical onset of the disease.\(^2\) High levels of GAD-Ab are found in the serum and cerebrospinal fluid (CSF) of at least 60% of patients with the stiff-man syndrome, a rare disorder of the central nervous system characterized by progressive muscle rigidity with superimposed painful spasms.\(^3,4\) Patients with stiff-man syndrome who have GAD-Ab usually also have IDDM and other organ-specific autoimmune manifestations, suggesting that the stiff-man syndrome may have an autoimmune-mediated pathogenesis.\(^5\) The GAD-Ab of patients with stiff-man syndrome are in higher titer and have a different epitope specificity than those of patients with IDDM, suggesting that the 2 diseases may have different autoimmune mechanisms.\(^6,7\)

Recent studies show that high levels of GAD-Ab may also be observed in a few patients with cerebellar ataxia, supporting an autoimmune pathogenesis of the cerebellar syndrome.\(^8-14\) To confirm this clinical-immunologic association, we describe a series of 14 patients with idiopathic cerebellar ataxia and high titers of GAD-Ab.

RESULTS

CLINICAL FEATURES

The main clinical features of the 14 patients with GAD-Ab and cerebellar ataxia are summarized in Table 1 and Table 2.


PATIENTS AND METHODS

PATIENTS AND SERUM SAMPLES

Serum samples were selected from those sent to 4 European laboratories (Barcelona, Spain; Lyon and Saint-Etienne, France; and Padua, Italy) to test for the presence of antineuronal autoantibodies associated with paraneoplastic neurologic syndromes. The selection criteria was an immunohistochemical pattern compatible with GAD-Ab. The presence of GAD-Ab was confirmed by radioimmunoassay (RIA) in 2 centers. Thirty-six serum samples from more than 9000 showed an immunohistochemical pattern compatible with GAD-Ab; 22 of them were from patients with typical stiff-man syndrome and the other 14 had ataxia as the predominant neurologic symptom. None of the selected serum samples had anti-Hu, anti-Yo, anti-CV2, anti-Tr, or anti-Ri antibodies. The clinical features of these 14 patients were obtained by personal clinical interview and neurologic examination, to establish the presence of a personal or familial history of autoimmune disorders and evolution of ataxia. Samples of CSF were obtained from all patients for standard examination and the presence of IgG oligoclonal bands. In 6 patients, paired serum-CSF samples were available to analyze a possible intrathecal synthesis of GAD-Ab.

To standardize the immunologic data, serum and, when available, CSF samples of the 14 patients were reevaluated by the techniques described below. The samples detected by immunohistochemical analysis were sent to the different laboratories with positive and negative controls (20 with idiopathic late-onset cerebellar ataxia and no anti-GAD reactivity by immunohistochemical analysis; 9 with polyendocrine autoimmunity [IDDM and thyroiditis] without neurologic symptoms and selected for presenting high GAD-Ab levels by RIA; 91 healthy subjects; 10 patients with stiff-man syndrome; and 49 with recent diagnosis of IDDM) and tested without awareness of the clinical diagnosis.

IMMUNOHISTOCHEMICAL ANALYSIS

Immunohistochemical analysis was performed on frozen sections of paraformaldehyde-fixed rat cerebellum by means of an avidin-biotin immunoperoxidase (Barcelona’s laboratory) and indirect immunofluorescence technique (Lyon’s laboratory) as previously described. An intrathecal synthesis of GAD-Ab was determined by means of the reciprocals of end-point titers determined by immunohistochemical analysis of paired serum-CSF samples and applying the Schüller formula as previously described. A ratio greater than 2 was considered positive for intrathecal synthesis.

IMMUNOBLOT

Immunoblots were done in Barcelona with a technique previously described. Briefly, human GAD65 recombinant protein (CIS Biointernational, Gif-sur-Yvette, France) (0.16 µg per lane) was electrophoretically separated in a 10% sodium dodecyl sulfate–polyacrylamide gel and transferred to nitrocellulose. Strips were sequentially incubated with the patient’s serum or GAD-6 monoclonal antibody (Hybridoma Bank, Iowa City, Iowa), immunoreacted with an avidin-biotin technique, and developed with diaminobenzidine tetrahydrochloride (Sigma-Aldrich Corp, St Louis, Mo).

RADIOIMMUNOASSAY

To confirm the anti-GAD specificity of the serum samples that were positive on immunohistochemical analysis, RIAs were performed with GAD labeled with iodine 125 obtained from 1 of 2 sources (CIS Biointernational or RSR Ltd [Cardiff, Wales]). In the Barcelona laboratory GAD was used according to the manufacturer’s instructions; in the Oxford, England, laboratory slight modifications were made as previously described.

DETECTION OF OTHER AUTOANTIBODIES

Serum samples from the 14 patients with ataxia who had GAD-Ab and the 20 patients with idiopathic late-onset cerebellar ataxia and no anti-GAD reactivity by immunohistochemical analysis were tested in the Lyon laboratory for the presence of other organ-specific autoantibodies. Antineural, antienidomyositis, antiantidrenalin, antipituitary, and antistomach autoantibodies were detected by an indirect immunofluorescence technique as previously described. Antithyroperoxidase, antithyroglobulin, antithyroglobulin, and anti-parietal cell autoantibodies were detected by enzyme-linked immunosorbent assay commercial kits according to the instructions of the manufacturers (Pharmacia Upjohn Diagnostics, Uppsala, Sweden, and Sigma Chemical Co, Paris, France). The IA2 antibodies were detected by radioligand assay.

and include 4 patients (patients 1-4) who were previously described. Thirteen of them were women, with a median age of 51 years (range, 20-74 years) at the onset of the cerebellar syndrome. Six patients had a family history of autoimmune diseases such as IDDM or thyroiditis, but none had a family history of cerebellar ataxia. Ten of 14 patients had IDDM. In all cases, these patients had a late-onset IDDM that started at a median age of 47 years (range, 28-66 years). The diagnosis of IDDM antedated the onset of the cerebellar syndrome in 7 patients (median, 8 years; range, 2-12 years). Other autoimmune disorders were thyroiditis (Hashimoto or Graves disease) (8 patients), pernicious anemia (2 patients), myasthenia gravis (1 patient), and psoriasis (1 patient). An asymptomatic celiac disease was diagnosed by duodenal biopsy in 1 patient after antigliadin autoantibodies were detected by a systematic test. Two patients presented with thymoma 3 years before and 2 years after the diagnosis of the cerebellar ataxia.

The cerebellar ataxia that developed in these 14 patients was similar (Table 2). A subacute onset was observed in only 1 case, whereas symptoms progressed slowly, suggesting a degenerative disease, in 13 patients. The main cerebellar sign, which was present in all of the patients, was gait ataxia that was moderate or severe in 10. Limb ataxia was also observed in 12 patients, but was rated as mild in 7. The cerebellar symptoms prevented a completely independent way of life (Rankin

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score, >2) in 10 patients. Nystagmus was observed in 12 patients and dysarthria in 8. Associated neurologic symptoms were leg rigidity suggesting a focal stiff-man syndrome (2 patients), peripheral neuropathy (1 patient), and myasthenia gravis (1 patient). The CSF examination gave normal results in only 4 patients. For the 10 other patients, CSF analysis showed a normal protein level, but isoelectric focusing and immunoblot of IgG detected oligoclonal IgG bands not present in the serum. Three patients had a high IgG index. Only 1 patient had an abnormal cell count (7 lymphocytes).

Magnetic resonance images of the brain were normal in 7 patients and showed pure cerebellar atrophy in the others. One patient had an associated Arnold-Chiari type 1 malformation (patient 4), but none showed brainstem atrophy.

**IMMUNOLOGIC STUDIES**

The RIA confirmed anti-GAD reactivity observed by immunohistochemical analysis in all 14 serum samples by the 2 laboratories with complete agreement. A positive

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**Table 1. Autoimmune Features in Patients With Cerebellar Ataxia and GAD-Ab**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Type of Onset</th>
<th>Rankin Score</th>
<th>Ataxia, Gait/Limb</th>
<th>Nystagmus</th>
<th>Dysarthria</th>
<th>Other Symptoms</th>
<th>MR Imaging</th>
<th>CSF Oligoclonal Bands</th>
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<td>5</td>
<td>++/+++</td>
<td>Yes</td>
<td>Yes</td>
<td>Peripheral neuropathy</td>
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<td>No</td>
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<td>++/++</td>
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<td>Yes</td>
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<td>Yes</td>
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<td>Yes</td>
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<td>1</td>
<td>++</td>
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<td>Normal</td>
<td>No</td>
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<td>++/+</td>
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<tr>
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<td>++</td>
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<td>Yes</td>
<td>Myasthenia gravis</td>
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<td>3</td>
<td>++</td>
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<td>++</td>
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<td>Yes</td>
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</table>

*GAD-Ab indicates antibodies to glutamic acid decarboxylase; NA, not applicable; and minus signs, negative.
†Diabetes was insulin dependent in all patients with diabetes.

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**Table 2. Neurologic and CSF Characteristics of Patients With Cerebellar Ataxia and GAD-Ab**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Duration, y</th>
<th>Type of Onset</th>
<th>Rankin Score</th>
<th>Ataxia, Gait/Limb</th>
<th>Nystagmus</th>
<th>Dysarthria</th>
<th>Other Symptoms</th>
<th>MR Imaging</th>
<th>CSF Oligoclonal Bands</th>
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<td>20</td>
<td>Insidious</td>
<td>5</td>
<td>++/+++</td>
<td>Yes</td>
<td>Yes</td>
<td>Peripheral neuropathy</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>Insidious</td>
<td>5</td>
<td>++/++</td>
<td>No</td>
<td>Yes</td>
<td>None</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
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<td>3</td>
<td>Subacute</td>
<td>4</td>
<td>++/+</td>
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<td>Yes</td>
<td>None</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
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<td>9</td>
<td>Insidious</td>
<td>3</td>
<td>/+</td>
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<td>Yes</td>
<td>None</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
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<td>10</td>
<td>Insidious</td>
<td>1</td>
<td>++</td>
<td>Yes</td>
<td>Yes</td>
<td>None</td>
<td>Normal</td>
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</tr>
<tr>
<td>6</td>
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<td>Insidious</td>
<td>4</td>
<td>++</td>
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<td>None</td>
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</tr>
<tr>
<td>7</td>
<td>4</td>
<td>Insidious</td>
<td>5</td>
<td>++/+</td>
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<td>No</td>
<td>None</td>
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<td>Yes</td>
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<tr>
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<td>+/−</td>
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<td>No</td>
<td>Rigidity in right leg</td>
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<td>Yes</td>
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<tr>
<td>9</td>
<td>3</td>
<td>Insidious</td>
<td>3</td>
<td>++</td>
<td>Yes</td>
<td>Yes</td>
<td>Myasthenia gravis</td>
<td>Normal</td>
<td>Yes</td>
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<tr>
<td>10</td>
<td>2</td>
<td>Insidious</td>
<td>2</td>
<td>/+</td>
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<td>None</td>
<td>Normal</td>
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<tr>
<td>11</td>
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<td>Insidious</td>
<td>3</td>
<td>++/+</td>
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<td>No</td>
<td>None</td>
<td>No</td>
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<tr>
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<td>Insidious</td>
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<td>++</td>
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<tr>
<td>13</td>
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<td>++</td>
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<td>Rigidity in left leg</td>
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<td>++/+</td>
<td>Yes</td>
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<td>None</td>
<td>Normal</td>
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</tr>
</tbody>
</table>

*GAD-Ab indicates antibodies to glutamic acid decarboxylase; CSF, cerebrospinal fluid; MR, magnetic resonance; and Cb, cerebellar.
†1 indicates independent life, minor symptoms; 2, can only do basic daily activities; 3, needs some support for basic daily activities; 4 needs total support for basic daily activities; and 5, bedridden.
‡+ indicates mild; ++, moderate; ++++, severe; and −, absent.
intra-thecal synthesis of GAD-Ab was observed in 5 of the 6 patients who had paired serum-CSF samples available (median, 11.5; range, 2.9-16.4).

All 14 serum samples of patients with cerebellar ataxia had a high level of GAD-Ab by RIA (Figure 1). The mean (±SD) level of GAD-Ab in these patients (37 300±30 460 U/mL) was similar to the level in those with stiff-man syndrome (21 750±19 280 U/mL) and significantly higher than the level in those with a recent diagnosis of IDDM (48±112 U/mL) or with polyendocrine autoimmunity without neurologic disease (5828±9355 U/mL) (P<.001). However, in 6 of the 9 patients with polyendocrine autoimmunity, serum GAD-Ab levels overlapped with those of patients with cerebellar ataxia and GAD-Ab (Figure 1). None of the control patients with idiopathic late-onset cerebellar ataxia without GAD reactivity by immunohistochemical analysis or the normal subjects had GAD-Ab by RIA.

The 14 serum samples displayed a band in immunoblots of GAD65 recombinant protein probed with the serum of patients with cerebellar ataxia and antibodies to glutamic acid decarboxylase (GAD-Ab) (lanes 2-15) and cerebellar ataxia without GAD-Ab by immunohistochemical analysis (lanes 16-17). The immunoreactive bands have the same electrophoretic mobility as that recognized by GAD-6, a monoclonal antibody directed against GAD65 (lane 1). Serum dilutions of the positive control and patients with cerebellar ataxia and GAD-Ab were adjusted to the GAD-Ab level by radioimmunoassay. Lanes 2 to 4, 1:20 000; lanes 5 to 6, 1:10 000; lanes 7 to 17, 1:5000.

Figure 1. Levels of antibodies to glutamic acid decarboxylase (GAD) by radioimmunoassay (Barcelona, Spain), expressed in arbitrary units. 1 indicates controls (n=91); 2, patients with insulin-dependent (type 1) diabetes mellitus (n=49); 3, patients with polyendocrine autoimmunity (n=9); and 4, patients with cerebellar ataxia with GAD antibodies (n=14). The horizontal line represents the median value of the normal subjects plus 3 SDs.

Figure 2. Immunoblots of GAD65 recombinant protein probed with the serum of patients with cerebellar ataxia and antibodies to glutamic acid decarboxylase (GAD-Ab) (lanes 2-15) and cerebellar ataxia without GAD-Ab by immunohistochemical analysis (lanes 16-17). The immunoreactive bands have the same electrophoretic mobility as that recognized by GAD-6, a monoclonal antibody directed against GAD65 (lane 1). Serum dilutions of the positive control and patients with cerebellar ataxia and GAD-Ab were adjusted to the GAD-Ab level by radioimmunoassay. Lanes 2 to 4, 1:20 000; lanes 5 to 6, 1:10 000; lanes 7 to 17, 1:5000.

This study describes a series of patients with cerebellar ataxia and high titers of GAD-Ab. It is important to recognize this subgroup of patients because they may respond to immunotherapies. Previous case reports of cerebellar ataxia and high titers of GAD-Ab did not establish a clear relationship between the presence of GAD-Ab and the cerebellar ataxia.8-14 The presence in most of these patients of oligoclonal bands in the CSF, GAD-Ab intrathecal synthesis, and late-onset IDDM and other organ-specific autoimmune disorders clearly distinguishes them from those with other nonfamilial late-onset cerebellar ataxia.

All but 1 patient presented with an insidious cerebellar ataxia without brainstem involvement that would fit in the first group of Harding’s classification on idiopathic late-onset cerebellar ataxia10 and that corresponds to the old Marie-Foix-Alajouanine type of cerebellar degeneration.21 We did not observe clinical or radiologic evidence of brainstem involvement, suggesting in our patients an olivopontocerebellar atrophy. Two patients had rigidity of one leg not explained by corticospinal tract dysfunction. These patients probably had a focal form of stiff-man syndrome.22 The co-occurrence of stiff-man syndrome and cerebellar ataxia with high titer of GAD-Ab was also described in 2 other patients in the literature.11,23 These facts suggest an overlap between the 2 neurologic symptoms and further emphasize the association of GAD-Ab with both cerebellar ataxia and stiff-man syndrome and suggest common pathologic mechanisms.

The clinical and serologic data of our 14 patients favor an immune system dysregulation. All but 1 patient were women, and many had other organ-specific, mostly endocrine, autoimmune manifestations. Indeed, all but 2 patients had evidence of other autoimmune disorders. Late-onset IDDM was observed in 71% of patients, thy-
ropathy, and low prevalence of nystagmus.24,25 There-
ponderance of males, high frequency of peripheral neu-
sion in in vitro experiments with isolated rat cerebellar
cause a selective suppression of GABA-ergic transmis-
in 1 case of cerebellar ataxia, the GAD-Ab were able to
cause the intracytoplasmic antigen and why their actions are so selective compared with the wide-
spread distribution of GAD in the nervous system. An
alternative explanation could be that the high anti-GAD
titers reflect only the presence of a more complex im-
mune reaction against the nervous system that could
implicate a cell-mediated immune response directed against
GAD or other cerebellar antigens. Even if GAD is not the
key antigen, the immunologic profile of these patients and their predisposition to develop organ-specific auto-
imune manifestations, coupled with the presence of oli-
goclonal IgG bands in the CSF, suggests an immune-
mediated disorder as the most probable pathogenesis of the cerebellar dysfunction.

In conclusion, our findings support a link between GAD autoimmunity and some cases of idiopathic cer-

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dres); Department of Neurology, Hospital Virgen de las Nieves, Granada, Spain (Dr Maestre); Department of Im-
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